Cancer Immunology Research

Of Microbes and Microsatellites

Chloe E. Atreya and Alan P. Venook

A ubiquitous oral cavity microbe, *Fusobacterium nucleatum*, is increasingly being implicated in colorectal cancer pathogenesis. An article in this issue elucidates the differential association of *F. nucleatum* with tumor-infiltrating lymphocytes depending on microsatellite instability status. Cancer Immunol Res; 6(11); 1290–1. ©2018 AACR.

See article by Hamada et al., p. 1327.

A human's intestines are sometimes dismissed as merely a conduit through which solid waste can be transported and expelled. In reality, the intestines represent a vital organ that plays a central physiologic role in functions ranging from digestion to maintenance of fluid balance to regulating parts of our immune system to hosting the huge community of microbiota called the microbiome.

To state the obvious, studying the microbiome is a daunting challenge. It is estimated that the number of microbiota is about 36 trillion. The diversity of species is staggering, and its members may change depending on the components of a recent meal or a dose of antibiotics. New molecular and biostatistical tools and the advances in immunotherapy have fueled the recent surge in interest in the microbiome—but where to start?

Since 2012, a group of coauthors has focused their efforts on dissecting the role of one bacterium, *F. nucleatum*, found to be enriched in colorectal carcinomas compared with matched normal colons (1). Mima and colleagues discovered that the proportion of *F. nucleatum*–high colorectal cancers gradually decreases along the continuum from the cecum to rectum (2), which may contribute to the explanation for the recent recognition that patients with advanced colorectal cancer originating in the proximal (right-sided) colon have a worse prognosis as compared with patients with tumors originating in the distal (left-sided) colon. Other factors are also operative, such as a gradient distribution of tumor mutations and patterns of gene expression, which may relate to distinct embryologic origins (right colon from the midgut; left colon from the hindgut). Nevertheless, *F. nucleatum* associates with poor prognosis right-sided and microsatellite instability (MSI)–high colorectal cancers. Remarkably, *F. nucleatum* was also observed to persist in distant metastatic lesions, and even through successive passages in patient-derived xenograft models (3).

Meanwhile, colorectal cancer has also gained notoriety in the immunotherapy space, albeit for its extraordinarily low responsiveness to checkpoint inhibitors. Even colorectal cancers with intermediate or moderately high tumor mutation burden are impervious to these treatments. The 5% of metastatic colorectal cancers that are MSI-high are the exception, with an objective response rate to pembrolizumab or nivolumab of ∼30%. Beyond MSI, biomarkers of nonresponse or response to checkpoint inhibitors have remained elusive. And this is where the next chapter of *F. nucleatum* research begins.

Here, Hamada and colleagues report that the presence *F. nucleatum* is positively correlated with tumor-infiltrating lymphocytes (TILs) in non–MSI-high tumors and inversely correlated with TILs in MSI-high tumors (4). In non–MSI-high cancers with fewer neoantigens, the proinflammatory effects of *F. nucleatum* appear to dominate, promoting a lymphocytic reaction. In MSI-high tumors with abundant neoantigens, *F. nucleatum* appears to suppress the adaptive immune response. Although not yet directly evaluated, the implication is that the presence of *F. nucleatum* may explain why some MSI-high colorectal cancers are able to evade immune-checkpoint blockade.

Such provocative findings will surely inspire further microbiome research, ranging from detailed mechanistic analyses to comprehensive sequencing-based surveys. Moreover, studies like this one are ushering in a new era of colorectal cancer clinical trials. In the near future, expect to see a proliferation of human trials involving antibiotics, probiotics, prebiotics, dietary modifications, and fecal microbiotica transplants. Although *F. nucleatum* cannot possibly tell the whole story, this work does give us a hopeful glimpse at a future where cost-efficient complementary approaches may yield effective prevention strategies, as well as tunable means to maximize efficacy and mitigate toxicity of immuno- and cancer-directed therapies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Department of Medicine and Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, California.

Corresponding Author: Chloe E. Atreya, University of California, San Francisco, 550 16th Street, 6th Floor, Box 3211, San Francisco, CA 94158. Phone: 415-353-9888; Fax: 415-353-9931; E-mail: chloe.atreya@ucsf.edu

doi: 10.1158/2326-6066.CIR-18-0567

References

1. Kostic AD, Gevers D, Pedamallu CS, Michaud M, Duke F, Earl AM, et al. Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. Genome Res 2012;22:292–8.
2. Mima K, Cao Y, Chan AT, Qian ZR, Nowak JA, Masugi Y, et al. Fusobacterium nucleatum in colorectal carcinoma tissue according to tumor location. Clin Transl Gastroenterol 2016;7:e200.

3. Bullman S, Pedamallu CS, Sicinska E, Clancy TE, Zhang X, Cai D, et al. Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. Science 2017;358:1443–8.

4. Hamada T, Zhang X, Mima K, Bullman S, Sukawa Y, Nowak JA, et al. *Fusobacterium nucleatum* in colorectal cancer relates to immune response differentially by tumor microsatellite instability status. Cancer Immunol Res 2018;6:1327–36.